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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,960	10/31/2005	Michihiko Kataoka	21408 US C038435/0185946	4639

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
10/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,960	KATAOKA ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *1-6, 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/22/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group III (claim 7), in the reply filed on 6/19/2008 is acknowledged.

The traversal is on the ground(s) that unity of invention exists between the groups I-IV. This is not found persuasive as explained bellow and therefore Groups I-II and VI (claims 1-6, and 8) of election/restriction-office action of date 04/23/2008 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups.

Applicants arguments of all claims belonging groups I-IV are linked by a special technical feature arguing that Wanner et al do not teach applicants' enone reductase have been fully considered but are not deemed persuasive to withdraw the restriction requirement previously applied. Enone reductase polypeptide encoded by DNA of claim 2(c) or claim 3(c) or claim 3(d) comprises a fragment of enone reductase of mwt ~61 kD and therefore is taught by Wanner et al. Further evidence that the claims lack special technical feature is found in rejection heading under U.S.C.102 below. Therefore the restriction is maintained and made FINAL.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 03/22/2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the IDS statement.

Priority

Acknowledgement is made of applicants' PCT application PCT/EP03/10473 filed 09/19/2003 and foreign application European Patent Office (EPO) 02021098.5 filled 09/23/2002.

Objections

Claim 7 is objected for depending from a non-elected claim 6. Appropriate correction is required. For examination purpose only claim 7 will be interpreted as a method of production of levodione from ketoisophorone using a genus of enone reductase having any structure from any source having characteristics recited in claim 1: a molecular weight: about 61 kD, cofactor: NADPH and NADH, substrate specificity: alpha, beta-unsaturated ketone, optimum pH: 4.5-8.5.

35 U.S.C 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 7, the phrase "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

35 U.S.C 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of production of levodione from ketoisophorone using enone reductase SEQ ID NO: 2, does not reasonably provide enablement for method of production of levodione from ketoisophorone using any enone reductase comprising a molecular weight of about 61 kD having any structure and characteristics recited in claim 1 (cofactor: NADPH and NADH, substrate specificity alpha, beta-unsaturated ketone, optimum pH 4.5-8.5) from any source. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

According to MPEP 2164.01(a), factors considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue"

include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP§ 2164.04 states that while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. Accordingly, the factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claim 7 recites a method of production of levodione from ketoisophorone using any enone reductase comprising a molecular weight of about 61 kD having any structure and characteristics recited in claim 1 (cofactor: NADPH and NADH, substrate specificity alpha, beta-unsaturated ketone, optimum pH 4.5-8.5).

The state of the prior art; The relative skill of those in the art; and The predictability or unpredictability of the art: It is well known in the prior art that the amino acid sequence of a protein determines the protein's structural and functional properties.

Predictability of which changes can be tolerated in a protein's amino acid sequence to obtain a desired enone reductase activity (convert ketoisophorone to levodione) requires knowledge and guidance regarding specific amino acid residue(s) in the protein's amino acid sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification) and detailed knowledge of the protein's structure, and the ways in which the protein's structure relates to its function. The reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug; 16(4):378-84) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships.

The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired enone reductase (convert ketoisophorone to of levodione) activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Methods for isolating or generating variants and mutants using random mutagenesis techniques were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the amino acid sequence of any enone reductase to obtain desired activity to

convert ketoisophorone to levodione and in the case of enone reductase of SEQ ID NO: 2, for altering the amino acid sequence with an expectation of obtaining a polypeptide having the same enone reductase activity. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the same desired biological activity. For example, the reference of Witkowski et al. (Biochemistry. 1999 Sep 7; 38(36): 11643-50) teaches that only a single amino acid substitution results in conversion of the activity of a polypeptide to a second, distinct activity (see e.g., Table 1, page 11647). In addition, the reference of Seffernick et al. (J Bacteriol. 2001 Apr; 183 (8): 2405-10) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; **DISCUSSION** section on page 2409).

The amount of direction provided by the inventor; and the existence of working examples: Claim 7 recites method of production of levodione from ketoisophorone using any enone reductase comprising a molecular weight of about 61 kD having any structure and characteristics recited in claim 1 (cofactor: NADPH and NADH, substrate specificity alpha, beta-unsaturated ketone, optimum pH 4.5-8.5). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enone reductase with variable structures broadly encompassed by the claim. The specification discloses one working example of such enone reductase comprising SEQ ID NO: 2 that isolated from *Candida kefyr*.

However, the specification fails to disclose any specific guidance for altering the amino acid sequence of any enone reductase or enone reductase of SEQ ID NO: 2 with expectation that the polypeptide will still have the same activity, because guidance and working examples teaching unalterable structural and catalytic amino acid residues and amino acid residues tolerable to change is not provided by the specification.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating and/or generating variants of a polypeptide were known in the art at the time of the invention and the specification provides general teachings for searching and screening for the claimed invention, it was not routine in the art to screen by a trial and error process for all polypeptides having a substantial number of modifications as encompassed by the claim(s) for those that maintain the same desired enone reductase activity. General teachings from the specification regarding screening and searching for the claimed invention using enzyme assays is not specific guidance for making and using the claimed invention.

Therefore, in view of the overly broad scope of the claims, the specification's lack of specific guidance and additional working examples, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, it would require undue experimentation for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)).

Without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988).

CLAIM Rejection - 35 U.S.C 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 7 is rejected under USC 102(b) anticipated by or in the alternative, under 35 USC 103 as obvious over by Vaz et al. (Biochem. 1995, 34, 4246-4256).

Claim 7 is directed to a method of production of levodione from ketoisophorone using an enone reductase comprising a molecular weight of about 61 kD on gel filtration (Mwt of 45000 on SDS gel electrophoresis, page 12 of the specification) comprising 400 amino acid residues (SEQ ID NO: 2) and having characteristics recited in claim 1 (cofactor: NADPH and NADH, substrate specificity: alpha, beta-unsaturated ketone, optimum pH: 4.5-8.5

Vaz et al. (Biochem. 1995, 34, 4246-4256) teach the use of old yellow enzyme (OYE1, an enone reductase that react on alpha, beta-unsaturated ketone using NADPH and NADH cofactor) for the reduction of olefinic bond and teach the conversion of ketoisophorone to levodione (Table 1 page 4252) at pH 7 and temperature 25^0 C and also teach the expression of OYE from *S. cerevisiae* in *E. coli*. The same old yellow enzyme used by Vaz et al. is characterized by Stott et al. (JBC 1993, 268, 6097-6106 from IDS) showing following characteristics: mwt of 47,000 by SDS gel electrophoresis, comprises ~400 amino acid residues and an amino acid sequence having 72% identical to applicants' enone reductase of SEQ ID NO: 2. A molecular weight of about 61 kD on gel filtration that taught by applicants enone reductase is an apparent mwt of fully formed and active enzyme. Molecular weight on gel filtration depends on the shape of the molecule as well as the degree of aggregation of the protein and is an approximate molecular weight. Applicants enone reductase shows Mwt of 45000 on SDS gel electrophoresis as a denatured protein (page 12 of the specification) and comprises 400 amino acid residues of SEQ ID NO: 2. Since the old yellow enzyme used by Vaz et al., which shows mwt of 47,000 by SDS gel electrophoresis, comprises ~400 amino acid

residues and which is 72% identical to applicants' enone reductase of SEQ ID NO: 2, Vaz et al. anticipate applicants invention of claim 7.

These rejection are being made under 35 USC 102(b) and 35 USC 103 because the examiner cannot distinguish the claimed method from that described by Stott et al. Applicants have the burden of distinguishing their claimed invention from that taught in the prior art by providing evidence that show the claimed method is different from that taught in the prior art. A preferred means of providing the evidence is for applicant to submit a side-by-side comparison between the enone reductase of the prior art and that of the instant application which demonstrates any material differences and shows the enone reductase used in the claimed method to be distinct and unobvious in view of the enone reductase of the prior art. *In re Best*, 430 USPQ (CCPA 1977) and *In re Fitzgerald*, 205 USPQ (CCPA 1980).

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 7 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 7 of US PAT 7202068. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 7 herein and claim 7 of the US PAT 7202068 are both directed to a method of producing levodione from ketoisophorone using enone reductase comprising a molecular weight of about 61 kD by gel filtration, Mwt of 45 kD on SDS gel electrophoresis and having following characteristics; cofactor: NADPH and NADH, substrate specificity alpha, beta-unsaturated ketone, optimum pH 4.5-8.5. The portion of the specification of the US PAT 7202068 that supports the recited method of producing levodione from ketoisophorone using enone reductase comprising a molecular weight of about 61 kD by gel filtration, Mwt of 45 kD on SDS gel electrophoresis and having following characteristics; cofactor: NADPH and NADH, substrate specificity alpha, beta-unsaturated ketone, optimum pH 4.5-8.5 would anticipate all of claim 7 herein.

Claim 7 cannot be considered patentably distinct over claim 7 of the US PAT 7202068 when there is a specifically recited embodiment (i.e. enone reductase

comprising molecular weight of about 61k, Mwt of 45 kD on SDS gel electrophoresis having characteristics of cofactor: NADPH and NADH, substrate specificity alpha, beta-unsaturated ketone, optimum pH 4.5-8.5 and method of use to convert ketoisophorone to levodione) that would anticipate claim 7 herein. Alternatively, claim 7 herein cannot be considered patentably distinct over claim 7 of US PAT 7202068 when there is a specifically disclosed embodiment in US PAT 7202068 that supports claim 7 of that application and falls within the scope of claim 7 herein because it would have been obvious to one having ordinary skill in the art to select the specific enone reductase that disclose in US PAT 7202068 and use it in the method of claim 7 of the US PAT 7202068 by selecting the specifically disclosed embodiment that supports claim 7. One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claim 7.

Conclusion

Claim 7 is rejected and no claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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